# Ethical issues in research with healthy volunteers: Risk-benefit assessment

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Most ethical commentary on clinical research concerns studies involving patient-subjects. Several reasons may account for the relative neglect of ethical appraisal of research with healthy volunteers. Clinical research is often understood ethically within the context of, or in contrast to, the physician-patient relationship characteristic of medical care.[1] In addition, research involving healthy volunteers is less likely to evoke ethical concern. Because these research subjects are not ill and, more specifically, do not have a condition with the potential to compromise decision-making capacity, there is no reason to question their ability to give informed consent. Similarly, they are free from the "therapeutic misconception" that causes some, perhaps most, patients to be confused about the differences between research participation and medical care.[2] Not being dependent on the advice of physicians, they are less likely than patients to feel pressure to participate in research. However, ethical concern has been focused on "coercion" or "undue inducement" associated with payment as an incentive for healthy volunteers to participate in research.[3] Moreover, the death in 2001 of a healthy research subject in a study aimed at understanding the pathophysiologic characteristics of asthma brought attention to the risks of research with healthy volunteers and to the imperative to ensure adequate subject protection.[4] The correspondence in this issue of the Journal regarding severe neutropenia among healthy clinical trial participants exposed to standard doses of rifabutin underscores the importance of scrupulous design and conduct of clinical investigation to protect research subjects.[5,6]

Research with healthy volunteers has particular ethical interest because it places in bold relief the moral context of all clinical research: Some individuals are exposed to risks of harm for the potential benefit of future patients and society.[7] From a medical perspective, healthy volunteers have no chance to benefit from research participation. The risks to which they are exposed can be justified only by the value of the knowledge to be gained from their research participation. A variety of clinical studies with healthy volunteers pose more than minimal risks of harm or discomfort. These include phase 1 trials of investigational drugs, psychiatric symptom-provoking studies,[8] infection challenge experiments,[9] and toxicology research involving monitored drug overdoses.[10] In this commentary I will focus on the pre-eminent ethical requirement of all clinical research, involving healthy or patient volunteers, that the research must pass the test of having a favorable risk-benefit ratio. Although informed consent is often considered to be the cornerstone of research ethics, informed consent does not come into play as an ethical requirement unless research is judged to have adequate potential value to justify any risks to which participants are exposed.[11]

It is important to recognize that risk-benefit assessment of research is primarily prospective. As Henry Beecher noted in 1966, "An experiment is ethical or not at its inception. It does not become ethical post hoc."[12] Obviously, the fact that valuable scientific knowledge may have resulted from abusive studies that exploited research subjects does not justify such research. The converse of Beecher's observation about prospective assessment is also relevant: Research does not become unethical post hoc. If a healthy volunteer dies as a result of research participation, this does not imply that the research was unethical. The most careful attention to study design and safety monitoring cannot eliminate remote chances of exposing healthy subjects to serious, irreversible harm. Because research involves experimentation under conditions of uncertainty, it cannot be

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risk-free and does not necessarily become unethical when it causes harm to research subjects.

All research aims at answering one or more questions. Accordingly, the scientific or social value of clinical research derives from the potential value that may accrue from answering specific research questions. Research subjects are exploited when they are enrolled in valueless research, especially because they must trust that investigators would not invite them to participate in a study that imposes burdens, inconvenience, discomfort, and even miniscule risks of serious harm if there were no potential scientific value to be achieved.

Satisfying the ethical requirement that a proposed research study has a favorable risk-benefit ratio involves the sequential steps of identifying the risks posed by research interventions, minimizing these risks, and judging that the potential benefits of the research to subjects and to society justify the risks. The identification of risks concerns the following three domains of assessment: probability, magnitude, and duration of harm. Accordingly, three questions must be addressed in assessing the level of risks posed by a study. First, what is the chance that interventions of the research protocol will produce various harms to the health or well-being of participants? Second, how serious is the potential harm from interventions of the study? Third, how long is the potential harm expected to last if it occurs? Risk assessment includes consideration of temporary discomfort or distress associated with research interventions, as well as lasting physical harm.

The requirement of minimizing risks of research involving healthy volunteers does not mean that these risks must be "minimal." Risks must be minimized within the context of designing and conducting valuable and rigorous clinical research. Accordingly, minimizing risks requires an inherently comparative assessment. A proposed research plan should be evaluated in the light of alternative ways to provide a rigorous answer to the scientific question that pose fewer risks to subjects. If the question can be answered by an alternative study design with fewer risks to subjects or without including a procedure that carries significant risks to subjects, then this alternative should be adopted or the unnecessary procedure omitted.

Multiple dimensions of the design and conduct of clinical research are relevant to the requirement of minimizing risks. Exclusion criteria for eligible participants should rule out those who can be predicted to be at increased risk from research interventions. Experimental procedures posing higher risks of physical harm or serious discomfort need to be carefully scrutinized to judge whether they are necessary to produce valuable data. Investigators must thoroughly review the literature to determine whether drugs or procedures proposed for use in research have been associated with serious adverse events and take steps to obviate or minimize such risks. Alternative, less risky ways to test study hypotheses should be explored. For example, imaging studies without the use of ionizing radiation, such as magnetic resonance imaging, are preferable to those that use radiation, such as positron emission tomography scans, provided that data of adequate quality can be obtained. When radiation use is scientifically necessary, the lowest dose needed to test research hypotheses should be administered. Finally, to minimize risks, careful procedures must be in place to monitor the condition of research participants and to intervene to counteract adverse events. Investigators should be prepared to end the study participation for particular subjects or terminate the study to protect subject safety.

After the risks posed by a proposed study are identified and care is taken to minimize risks, the final step of risk-benefit assessment is to determine whether the potential benefits of the knowledge to be gained by the research justify the risks to subjects. The Declaration of Helsinki, the leading international code of ethics for clinical research, states that "Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers."[13]

A difficult issue of risk-benefit assessment is whether there exists an upper threshold on allowable risk for research involving healthy volunteers. Certainly, as the risks from proposed studies increase, the potential knowledge value needed to justify these risks must also increase. Are some studies too risky to conduct no matter how much potential benefit in clinically relevant knowledge they offer? Neither the US federal regulations governing human subjects research nor the Declaration of Helsinki places any determinate limits on the risks to which research participants can be exposed. The Nuremberg Code, developed in the wake of the brutal Nazi concentration camp experiments, states the following: "No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects."[14] The code does not make clear what antecedent probability of death or disabling injury from research interventions should rule out a study enrolling healthy volunteers.

Consider the following example. In view of the current public concern about the possible use of smallpox as a weapon of bioterrorism, it might be of considerable scientific and social value to develop improved vaccines against this infectious disease. To speed the development of a candidate vaccine, would smallpox challenge studies administering the virus to human volunteers be ethically justifiable, given that no effective treatment exists and the mortality rate from the disease is estimated to be approximately 30%? It is unlikely that any funding agency or institutional review board (IRB) would endorse such an experiment. However, it is worth pondering whether the famous experiments in healthy volunteers conducted by Walter Reed on the transmission of yellow fever—a potentially lethal disease without treatment—would be considered ethical by our contemporary standards. The Nuremberg Code's hesitant qualification about the allowable level of risk when investigators also serve as subjects was probably introduced with an eye to Walter Reed's research. In any case, whether there should be a limit on acceptable risks for healthy volunteers regardless of the magnitude of potential value from a proposed study remains an unsettled issue of research ethics.

How can it be determined whether the potential value of knowledge to be gained from a given study can justify the risks posed to research subjects? There are no formulas available. The assessment calls for carefully considered and deliberated judgments by research sponsors, investigators, and IRBs.

Healthy research subjects trust that investigators would not invite them to participate in research and that IRBs would not approve the research if it would knowingly expose the subjects to substantial risks of serious harm. To be worthy of that trust and to protect research subjects, investigators and IRBs must be conscientious in risk-benefit assessment of all research involving human subjects.

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